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The history of organ transplantation

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ABSTRACT

Since ancient times, mythology has included tales of creatures made of an amalgamation of others, transferring body parts and skin. In the 1950s, with no other medical options for then incurable diseases, including nephritis, teams of scientists, surgeons, and generous patients started the field of organ transplant with the first successful kidney transplant in a human. The scientific discoveries and innovations since that first successful transplant in 1954 have turned the mythical concept of transplant into reality. The overall success and public acceptance of organ donation and transplant today is thanks to multidisciplinary teams of basic scientists, immunologists, surgeons, and public advocates. Today, research is propelling the field forward with advancements like face transplants, experiments of lab-grown organs, and much more. In the United States alone, over 800,000 patients have had their lives saved or significantly improved thanks to transplant since national recording began by the Organ Procurement and Transplant Network in 1988.

KEYWORDS History; surgery; transplantation

The idea of transferring body parts appears in ancient mythology of civilizations around the world. Roman, Greek, Indian, Chinese, and Egyptian legends include tales of organ transplants performed by gods and healers using organs from cadaveric and animal origins. Here we delve into the transformation of transplantation from lore to medical practice.

LORE

The first written mention of transplant is attributed to the Ebers Papyrus, written circa 1550 BC, which mentioned skin grafting for the treatment of burns.[1] Around 600 BC, the Indian surgeon Sushruta, known as the father of surgery, is credited with performing the first plastic surgery operations, including full-thickness skin grafts.[2] In "The Miracle of the Black Leg," from Jacobus De Voragine's 348 AD *Legenda Aurea*, limb transplantation was first mentioned in written literature. In this story, the Christian patron saints of medicine, pharmacy, and surgery, Cosmas and Damian, replace the cancerous leg of a Roman deacon with that of a recently deceased Ethiopian man.[3] In 1817, French physician Henri Dutrochet wrote a letter to the editor of *Gazette de Santé* on skin transplant, based on a story from his brother-in-law, an army officer stationed in India. According to the letter, an army subordinate had been punished by having his nose cut off. The man sought out locals well versed in skin grafting and known for their ability to surgically reconstruct a nose, and he asked them to operate on him.

> Because the defect was already showing cicatrization, the wound edges were freshened. One of the man's buttocks, which was to be the donor site, was beaten with an old shoe until a substantial swelling was achieved. From this swollen area, a triangular piece of skin, with subcutaneous fat, was then cut and placed on the defect. It was fixed in position with adhesive plaster. The graft healed, and the man continued to serve in the brother-in-law's command.[4]

While there is uncertainty regarding the veracity of Dutrochet's letter, other sources have documented the practice of skin grafting in India hundreds of years earlier.[5] Despite the doubt of whether these ancient surgeries took place as described, the accounts demonstrate long-standing fascination with transplanting body parts from one person to another. Only in recent history have these ideas of transplant become reality.

MODERN MEDICINE

The first verifiably documented skin transplant occurred in 1869. Swiss surgeon Jacques-Louis Reverdin demonstrated

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success with epidermic grafting, in which he used small samples of epidermis pinched or shaved off superficial layers of skin. Pinch grafting is still used to expedite formation of granulation tissue and improve survival of larger skin grafts. Skin grafts continued to be used in burn treatment until World War I. For a short time, ointment treatments and use of tannic acid replaced grafts,[6] but by World War II, it was discovered that tannic acid caused liver necrosis, and grafting again became common practice.[7,8]

A particularly notable patient treated during World War II was a pilot, Charles Woods. On December 23, 1944, Woods set off with a load of 28,000 pounds of aviation fuel, which exploded on takeoff. He suffered severe burns over 70% of his body, including his face. The injury appeared to be nonsurvivable. However, 6 weeks after the accident, the medical team at the Valley Forge General Hospital in Pennsylvania grafted skin onto Woods from a recently deceased soldier. This graft was successful; "possibly because of his debilitated condition, his immune response had been tamed."[9] After 24 more operations over the next 2 years, Woods returned to a relatively normal life and went on to have a family and become a businessman. He died in 2004 at the age of 84.

One of the physician members of Woods' medical team was Joseph Murray. After finishing his surgical internship year, Murray was inducted into the US Army Medical Corps and stationed at Valley Forge. After the war, Murray returned to his surgical training at the Peter Bent Brigham Hospital in Boston. Having seen the success of Woods' case, Murray was fascinated by transplantation, especially of organs. Despite a general consensus that transplantation of anything other than skin was not feasible due to rejection, Murray "knew something had tamed Woods's immune system. So transplantation did not seem a futile quest to [him]."[9]

KIDNEY TRANSPLANT

By the 1950s, skin grafts had been the only successful transplants performed, but basic science had been researching the viability of transplanting organs. Much of early organ transplant research focused on kidneys, since live donors, the only kind at the time, could survive with just one of their own. In 1953, 22-year-old Richard Herrick was discharged from the Coast Guard with chronic nephritis, a then life-threatening diagnosis with no cure. At this time, there had been other renal transplants in humans that had proven unsuccessful: the first renal human allograft was performed on April 3, 1933, by Dr. Yurii Voronoy in Ukraine.[10] In this case, the patient survived for 2 days, and the failure of the case is largely attributed to ABO incompatibility and prolonged warm ischemia time of the kidney. Other surgeries had also been performed in Boston, Chicago, and Paris.

Although renal transplants had been unsuccessful thus far, Herrick went to Murray for help, as Murray had been developing his own techniques necessary to perform a renal transplant. With a dire condition and a healthy twin brother, Herrick agreed to undergo the experimental procedure, receiving a kidney from his twin. Murray and his colleagues tested the matching of the brothers by performing small skin grafts from each brother to the other, and they even fingerprinted the two to confirm that they were identical.[11] The Herrick brothers underwent surgery without complications exactly 10 years after Woods' plane had exploded. Herrick went on to marry one of his nurses, have two children, and live another 8 years with his brother's kidney, the first ever successfully transplanted organ.

In 1959, the first kidney transplant in Louisiana was performed at Charity Hospital. This case marked the first successful kidney transplant between individuals not genetically identical. The donor and recipient were fraternal twin brothers. At the time, immunosuppression had not yet been added to transplantation care. Before receiving his brother's kidney, the recipient underwent a sublethal, non–marrow-requiring dose of total body x-ray. At this time, "the exact role of the X-irradiation in these patients ha[d] not yet been assessed with certainty because the fate of a kidney transplant between dizygotic twins without the use of total body irradiation [wa]s not known."[12] Despite a difficult postoperative recovery, the patient continued living an active life and died of cardiac issues 25 years later. This success excited transplant teams across the world.

By the 1960s, it was clear that not all transplants could be from genetically identical or even related donors, so research scientists and physicians delved into immunosuppression to prevent rejection. In 1962, Dr. Roy Calne and his team at Peter Bent Brigham Hospital published findings that 6-mercaptopurine prolonged survival after renal transplant in 104 dogs.[13] Murray and his team transitioned Calne's experiment from their lab to human patients in the hospital. They found that irradiation conferred little benefit alone, while chemical suppressive agents azathioprine, actinomycin C, and prednisone improved at least short-term outcomes. This "permit[ted] a cautious optimism in a problem that ten years ago was considered almost insoluble."[14] These cautiously optimistic results would lead to an expanded donor pool, as the immune reaction to foreign organs could be suppressed. In 1962, Murray led the first renal transplant between nonrelated patients with the use of azathioprine. This was also a landmark case, as it was the first successful transplant from a deceased donor.

Until now, successful transplants had been allografts, human to human. Between November 5, 1963, and February 4, 1964, six patients received renal chimpanzee xenotransplants.[15,16] Dr. Keith Reemtsma and the multidisciplinary transplant team at Tulane University had begun to investigate nonhuman sources for renal transplants due to a scarcity of donated kidneys.

> In our renal homografting program we had increasing difficulty obtaining donor organs. Attempts to use cadaveric kidneys met with no prolonged success, and the supply of expended kidneys was inadequate. We were reluctant to press the use of volunteer humans for ethical, scientific and legal reasons.[15]

Prior reports of xenotransplant at the time included renal transplants from a rabbit to a child in 1905,[17] from pig and

goat into the antecubital space in 1906,[18] and from a lamb to a human in 1923.[19] All of these cases were met with failure within days due to patient death or graft thrombosis. Despite the lack of prior success with xenotransplantation, Tulane's proximity to the regional primate center and primatologists made exploring primate-to-primate renal transplant feasible. Chimpanzees were selected as the donor species due to their close taxonomical relationship, similar size, comparable renal function,[20] and their A and O blood types, which allowed universal donor potential.[21] The patients who received chimpanzee kidneys lived from 11 days to 9 months posttransplant, and the outcomes were viewed as an overall success by the transplant community. Two of these patients experienced early signs of suspected rejection, which was reversed with increased immunosuppression. Sepsis proved a more common and lethal complication, along with acute electrolyte abnormalities. Despite further attempts from around the world, chimpanzee- and baboon-to-human renal and cardiac transplants never achieved long-term patient survival. Tulane subsequently developed a successful cadaveric organ procurement program and discontinued its xenotransplant clinical activities in 1965, but continued basic science research on the topic.

Until the 1960s, cadaveric organs were retrieved from patients who had died of cardiac death, the only recognized type of death at the time. In 1959, Dr. Guy Alexandre, a Belgian surgeon who had been one of Murray's research fellows at Harvard, introduced the idea of *coma dépassé,* a state beyond the deepest type of coma.[22] Coma dépassé was made possible by artificial ventilation, which preserved oxygenation to organs in patients with no brain function who would have otherwise expired due to respiratory arrest. On June 3, 1963, a patient with a severe head injury was brought to the Hôpital Saint-Pierre in Brussels. Despite all resuscitation efforts, the patient was in a state of coma dépassé. Alexandre's request to perform a renal transplant with a kidney from this "beating-heart donor" was approved by the department chair, and this first donation after what we now know as brain death was a success.

TRANSPLANT OF OTHER ORGANS

While the early years of transplantation focused largely on kidneys, by the late 1960s, liver, heart, and pancreas transplants from deceased donors had also been performed successfully. After performing more than 400 lung transplants on dogs, Dr. James Hardy's team at the University of Mississippi transplanted the first human lung from a non-heart-beating donor in 1963. The recipient, who had received the transplant due to his diagnosis of bronchial carcinoma, died 18 days postoperatively.[23]

The first experimental liver transplant by Dr. Stewart Welch was performed on a dog and involved placing the donor liver into the abdomen without the removal of the native liver, or heterotopically.[24] Portal inflow insufficiency caused graft failure, which at the time was attributed to liver-mediated rejection. In subsequent surgeries, the donor liver replaced the original organ. While removing the liver did not prevent rejection, this orthotopic technique remains the standard today. In 1967, Dr. Thomas Starzl performed the first liver transplant in a human at the University of Colorado, aided by canine model results and azathioprine and steroid-based immunosuppression.[25] The first three patients survived between 7 and 22 days.[26,27] Starzl and Calne refined surgical techniques, organ preservation, and immunosuppression through the 1970s, as 1-year survival rates remained below 25%. This continued investigation and the discovery and clinical use of cyclosporine in the late 1970s increased long-term survival.

Dr. Christiaan Barnard, a South African cardiothoracic surgeon, and his brother, a fellow cardiac surgeon, practiced in dogs the cardiac transplant techniques that had been developed by Dr. Norman Shumway at Stanford University. Barnard took a sabbatical at the University of Virginia to gain experience with immunosuppression used in renal transplant patients. After performing a successful renal transplant back in Cape Town, Barnard attempted the world's first heart transplant. South African law was vague, in that it only stated that a patient was dead after a physician had declared death. Barnard declared 25-year-old Denise Darvall dead with brain-death criteria after an accident with an automobile caused her irreversible head injury. Barnard detached the ventilator and waited until the electrocardiogram indicted absence of cardiac output, approximately 6 minutes.[28] The recipient, Louis Washansky, who had been bedridden with diabetes, ischemic heart disease, and heart failure, died 18 days postoperatively. Barnard's subsequent patients had better results; the second led an active life for almost 19 months, and the fifth and sixth patients lived for 12 and 24 years, respectively.

While these surgeries were great successes and unimaginably incredible to the world, some raised the question of whether removal of the heart was responsible for killing the donors. Just 1 month after Barnard's monumental first human heart transplant, Dr. Norman Shumway performed the first human heart transplant in the US. During surgery, his chief resident assisting him asked, "Do you think this is really legal?" Shumway simply responded, "I guess we'll see."[29]

After his own father died due to heart disease, Dr. Robert Jarvik invented an entirely new technology for the transplant field. At the University of Utah, Jarvik designed a totally artificial heart, the Jarvik-7. In 1982, Dr. William DeVries and his team under Dr. Reemtsma, then at the University of Utah, spent 7 hours in the operating room implanting the Jarvik-7, the first total artificial heart implant in a human. This version of implant required the patient to be attached to a 350-pound air compressor, and the patient lived in the hospital for 112 days. The Jarvik-7 was implanted in more than 150 patients during the 1990s when

their hearts were too damaged for other interventions until donors were identified.

VASCULARIZED COMPOSITE GRAFTING

In 1998, the new immunosuppressants tacrolimus and mycophenolate mofetil improved recipient tolerance of transplants, especially vascularized composite grafts composed of multiple tissues. The same year, Dr. Jean-Michel Dubernard in Lyon, France, performed the first successful hand transplant on a patient with a mid-forearm amputation. Dubernard later performed the first double hand transplant in 2000.[30] In 2005, Dr. Bernard Devauchelle and Dubernard performed a partial face transplant on Isabelle Dinoire, who had suffered a disfiguring dog attack 7 months earlier and felt she could not return to normal life. Until then, facial reconstruction was the only surgical option for patients like Dinoire with deformities due to accidents, burns, war, tumor ablative surgeries, and other trauma. Reconstruction has both cosmetic and motor function limits and patients with particularly complex deformities may not be responsive to or eligible for these procedures. In 2010, a Spanish team led by Dr. Juan Barret performed the first full-face transplant.[31] This represents a culmination of the progress made by the field which was, in part, pioneered by Murray after he saw success in Woods' facial grafts 77 years earlier.

ORGANIZATION AND PUBLIC SUPPORT OF TRANSPLANT

Regulation and organization has helped transplant become widely accepted with the public. The first significant governmental involvement in transplant was the National Uniform Anatomical Gift Act, drafted in 1967. This allowed individuals or next-of-kin to donate organs and/or tissue for transplantation at the time of death and created the uniform donor card. The medical community itself had to make decisions on aspects unique to the field of transplant. Although Alexandre had performed a transplant from a coma dépassé patient 5 years earlier, official criteria for brain death were established in 1968 by a committee at Harvard Medical School. The report aimed to define irreversible coma as a criterion for death in order to lessen burdens of permanently comatose patients on families and hospitals and clear up controversy in obtaining organs for transplantation. Donation after brain death has become the most common form of donation.

Through the late 1960s, each transplant center was individually responsible for finding donors and recovering organs. Centers established organ banks, which ran donor logistics. If a potential donor did not match any recipients at that transplant center, there was no way to match organs with recipients elsewhere. Murray founded the New England Organ Bank to serve 10 transplant centers in the area. The success of the organ bank spurred other areas to do the same. These networks allowed the gifts of a single donor to reach more recipients further away. In 1977, the South-Eastern Organ Procurement Foundation (SEOPF) established a computer database to increase efficiency of matching organs to a compatible patient at any member institution. This database, called the United Network for Organ Sharing (UNOS) database, was revolutionary. SEOPF opened a Virginia call center in 1982, which has been operating continually since and today is the UNOS Organ Center.

In 1984, the National Organ Transplant Act created a national network for allocation of organs and collection of data on donation, transplant, and patient outcomes. In 2013, donor criteria expanded to include a larger pool of potential matches for recipients. Once excluded from donating, individuals with human immunodeficiency virus can now donate to patients with the same viral status. Current hepatitis C treatment allows for transplantation of hepatitis C–positive organs and subsequently treatment and cure.

Currently, over 110,000 patients in the United States are on the UNOS waiting list for an organ transplant that can either save or dramatically improve their life. The ever-evolving science behind transplant has been a success thanks to experts in basic science, immunology, surgery, biology, and transplantation. Although the history behind the field is short in terms of years, it is full of medical marvels. The first successful human transplant occurred in Boston in 1954, not even 70 years ago. While met with public trepidation in the early years, the cause has become an exemplar of a process championed by science and public education, bringing acceptance and support. Since the Organ Procurement and Transplant Network began recording information about organ transplants in the United States in 1988, over 800,000 transplants have been performed in the US alone.[32] In the past 68 years, scientists, doctors, and patients have transformed transplantation from mythology into reality. Only time will tell where the next 68 years will bring us.

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